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(21) International Application Number: PCT/SE97/00566 (22) International Filing Date: 1 April 1997 (01.04.97) (30) Priority Data: 9601421-2 12 April 1996 (12.04.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BRODIN, Ame [SE/SE]; Kämpervägen 24, S-151 54 Södertälje (SE). FYNES, Ray- mond [CA/CA]; 1540 Troika Court, Mississauga, On- tario L5J 4O4 (CA). HEIJL, Lars [SE/SE]; Hammarströms Täppa 5 B, S-443 39 Lerum (SE). NYQVIST-MAYER, Adela [SE/SE]; Eklidsvägen 20, S-146 40 Tullinge (SE). SCHERLUND, Marie [SE/SE]; Tackjärnsvägen 12, S-161 31 Bromma (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: NEW PHARMACEUTICAL COMPOSITION WITH ANAESTHETIC EFFECT (57) Abstract The invention is directed to a novel pharmaceutical composition comprising one or more local anaesthetics in oil form, one or more surfactants, water and optionally a taste masking agent. The novel composition is advantageously used as a local anaesthetic for pain relief within the oral cavity.		

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NEW PHARMACEUTICAL COMPOSITION WITH ANAESTHETIC EFFECT

The field of the invention

5 The present invention is directed to a new pharmaceutical composition and its use in therapy, particularly as an anaesthetic for use on mucous membranes and particularly within the oral cavity.

10 Background and prior art

It is estimated that approximately 10-13 % of the population suffers from periodontal diseases with pathological periodontal pockets. In order to eliminate or control the disease and arrest further periodontal tissue destruction, periodontal pockets need repeated
15 subgingival mechanical debridement/cleansing. The number of periodontal pockets in a patient may vary as can the pocket depth measurement. Approximately 40 % of all periodontal scaling procedures performed involve some kind of anaesthesia.

Accumulation of bacterial plaque on teeth and in the gingival sulcus elicits an inflammatory
20 response in the marginal gingiva which may spread in an apical direction and result in loss of tooth support with the formation of periodontal pockets. The object of mechanical debridement of periodontal pockets is to control and arrest further destruction of tooth support by removal of plaque and calculus from within the pockets.

25 The majority of the scaling procedures are performed by hygienists. The main use of anaesthesia techniques used in conjunction with periodontal scaling is either a nerve block or infiltration. Infiltration anaesthesia is either carried out alone or in combination with topical anaesthesia, mainly jelly, ointment or spray. However, the problem with existing
30 topical products are lack of efficacy due to inadequate depth of penetration, too short duration and difficulties in administration due to spread, taste etc.

EP 244 118 discloses a controlled release drug delivery system for placement in the periodontal pocket, having a plurality of discrete microparticles consisting of a rate-controlling polymer matrix having a drug dispersed therein, said microparticles being in the range of 10-500 μm . EP 241 178 also discloses a controlled release drug delivery system
5 for placement in the periodontal pocket, which composition comprises solid particles having an average size of 1-500 μm . However, the drug delivery systems disclosed in both these prior art patents are devised for administration of a medicament for a longer period of time. Thus the drug delivery systems of EP 244 118 and EP 241 178 are not suitable for use in pain management in conjunction with minor surgical procedures, where a fast onset of
10 action and relatively short duration is required.

Thus, the problem underlying the present invention is to provide a pharmaceutical composition which would provide effective pain relief in conjunction with periodontal scaling and root planing following local administration. In other words, the object of the
15 invention is to provide a local anaesthetic that can be applied in a facile manner in the oral cavity, and more precisely within periodontal pockets. A further object of the invention is to provide a pharmaceutical composition having a short onset time and an adequate duration for the intended procedure, with no inconvenient anaesthesia.

Outline of the invention

The problem identified above has now been solved by providing a new pharmaceutical
5 composition which preferably is in form of an emulsion, more preferably in form of a
microemulsion, comprising the following ingredients:

- (i) One or more local anaesthetics in oil form in the final composition;
- 10 (ii) one or more surfactants, together present in an amount effective to produce a
homogenous formulation; and
- (iii) water up to 100 % by weight, based on the total weight of the composition.

15

The local anaesthetic in the final composition is one or more local anaesthetics in oil form as
such, or a eutectic mixture formed by two or more local anaesthetics. The amount of the
local anaesthetic in the oil phase depends on the pH-value of the formulation.

20 In a particularly preferred embodiment of the invention the local anaesthetic is a eutectic
mixture of lidocaine base and prilocaine base.

In a further embodiment of the invention a eutectic mixture may also be formed by two or
more substances, where at least one of these substances is a local anaesthetic.

25

The amount of the local anaesthetic or mixture of local anaesthetics is preferably in the
range 0.5 - 20 % by weight, more preferably in the range 2-7 % by weight, based on the
total weight of the composition.

30 The local anaesthetic(s) in the final composition are present in a non-solid form.

By the wording "surfactant" we mean any agent that acts as a solubilizer and/or as an emulsifier and/or as a thickening agent with thermoreversible gelling properties. The wording surfactant is also intended to include thickening agents without thermoreversible properties. If only one surfactant is used in the composition, it must be selected with care and in suitable amounts so that it acts both as a solubilizer and/or as an emulsifier, as well as a thickening agent with thermoreversible gelling properties. If more than one surfactant is present in the composition, at least one of the surfactants should have thermoreversible gelling properties. The total amount of the surfactant(s) should be present in an amount effective to produce a homogenous formulation.

The surfactants are preferably selected from non-ionic surfactants, more preferably from any non-ionic poloxamer known in the art.

Poloxamers are synthetic block copolymers of hydrophilic ethylene oxide chains and

hydrophobic propylene oxide chains, having the general formula

$\text{HO}-(\text{C}_2\text{H}_4\text{O})_a-(\text{C}_3\text{H}_6\text{O})_b-(\text{C}_2\text{H}_4\text{O})_a-\text{H}$, a and b representing the number of the hydrophilic and hydrophobic chains respectively.

By choosing the surfactant(s) having hydrophobic and hydrophilic domains in appropriate amounts, in combination with an appropriate amount of the local anaesthetic or mixture of local anaesthetics, it is possible to achieve a composition having suitable thermoreversible gelling properties, i.e. the system remains less viscous at room temperature, and upon application into a periodontal pocket the viscosity of the composition is increased. In other words, the pharmaceutical composition according to the present invention is less viscous at room temperature. Above this temperature the composition is more viscous, providing the advantage of remaining in the periodontal pockets for the time necessary to induce local anaesthesia. The change in viscosity is reversible with temperature.

In a particularly preferred embodiment of the invention the surfactant is one or more of Lutrol F68[®], which also has the name poloxamer 188 and wherein a= 80 and b=27, and Lutrol F127[®], which also has the name poloxamer 407 and wherein a=101 and b=56, the
5 definitions being in accordance with USP (1995) NF18, p. 2279. Lutrol F68[®] and Lutrol F127[®] are commercially available from BASF.

In a further preferred embodiment of the invention the surfactant Arlatone 289[®] is used, which also has the name polyoxyethylene hydrogenated castor oil, as well as Adinol CT95[®]
10 which is sodium N-methyl N-cocoyl taurate.

The total amount of surfactant(s) is preferably present in an amount of up to 50 % by weight, based on the total weight of the composition.

15 The pH-value of the pharmaceutical composition is adjusted with suitable acid or base in such a way that the final pH-value for the composition is:

(A) $\text{pH} \geq [\text{pK}_a (\text{local anaesthetic}) - 1.0]$ if the composition comprises one local anaesthetic;
or

20 (B) $\text{pH} \geq [\text{pK}_a (\text{local anaesthetic with the lowest pK}_a \text{ value}) - 1.0]$ if the composition comprises two or more local anaesthetics.

Preferably the pH is over 7.5.

25 Since local anaesthetics by nature have an unpleasant bitter taste, one or more taste masking agents may optionally be added to the pharmaceutical composition. The choice of taste masking agents will be appreciated by a person skilled in the art, but as an example any fruit flavours may be mentioned.

By topical application within the periodontal pocket, local anaesthesia is achieved in a very localised area, without causing the often extensive soft tissues such as the tongue, cheek and lips, to get anaesthetized which is often the case with infiltration anaesthesia. Preferably
5 the composition is applied into a periodontal pocket by means of a blunt needle, thereby facilitating the administration of the anaesthetic and giving an increased patient comfort.

The pharmaceutical composition of the present invention has a fast onset of action being from seconds and up to approximately 5-15 minutes. The onset time is most preferably
10 from seconds and up to approximately 5 minutes.

For the definition of emulsions, we refer to *Pharmaceutics, The Science of Dosage Form Design, 1988, p. 109-110, by ME Aulton.*

15 The pharmaceutical composition according to the present invention is preferably a microemulsion. By microemulsion we mean a formulation that consists of water, oil and amphiphile(s) which constitute a single optically isotropic and thermodynamically stable liquid solution (*I. Danielsson and B Lindman, Colloids Surf. 3:391, (1981)*).

This provides a suitable amount of the local anaesthetic in the oil phase, which in turn
20 confers a fast onset of action. No separate oil needs to be added to the composition, since the oil is already present by the active component(s) as such. A further advantage is that a thermodynamically stable composition is achieved in a temperature range of 5-40 °C.

The pharmaceutical composition according to the present invention may advantageously
25 also be used as a local anaesthetic on other surfaces and/or cavities than in the oral cavity. The composition may thus also be used vaginally, genitally and rectally.

The local anaesthetic(s) used for preparing a pharmaceutical composition according to the present invention may be selected from any local anaesthetic. Preferably the local
30 anaesthetic as the starting material is in a non-ionized form.

In the final composition a fraction of the local anaesthetic or mixture of local anaesthetics are present in oil form. The size of this fraction, local anaesthetics in oil form, depends on the pH of the composition.

- 5 The best mode of performing the invention known at present, is to use the composition according to Example 1.

Methods of preparation

10

The pharmaceutical composition according to the present invention may be prepared by the following steps:

- (i) the local anaesthetic(s) and the surfactant with the lowest molecular weight if more than
15 one surfactant is used, are melted together;
- (ii) a part of the water is slowly added to the melt (i) during homogenization, forming an emulsion concentrate;
- 20 (iii) if more than one surfactant is used, the surfactant with the higher molecular weight is dispersed in water;
- (iv) the emulsion concentrate of step (ii) and part of the surfactant solution of step (iii) are thoroughly mixed;
- 25 (v) the pH-value is adjusted by the addition of a suitable acid or base;
- (vi) the weight is adjusted with water to the final weight of the composition.
- 30 The composition is preferably kept at 5 °C until a homogenous composition is obtained.

Detailed description of the invention

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

5

<u>Example 1</u>	<u>[% by weight]</u>
Lidocaine	2.50
Prilocaine	2.50
10 Lutrol F68 [®]	5.50
Lutrol F127 [®]	15.50

purified water up to a total weight of 100 %.

15 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

<u>Example 2</u>	<u>[% by weight]</u>
Lidocaine	2.50
Prilocaine	2.50
20 Lutrol F68 [®]	5.00
Lutrol F127 [®]	16.25

purified water up to a total weight of 100 %.

25 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 3 [% by weight]

Lidocaine 2.25

Prilocaine 2.25

5 Lutrol F68[®] 3.5Lutrol F127[®] 14.0

purified water up to a total weight of 100 %.

10 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 4 [% by weight]

Lidocaine 2.25

Prilocaine 2.25

15 Arlatone 289[®] 1.90Adinol CT95[®] 0.07

Lutrol F127 14.00

purified water up to a total weight of 100 %.

20 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

<u>Example 5</u>	<u>[% by weight]</u>
Lidocaine	2.25
Prilocaine	2.25
5 Arlatone 289 [®]	1.90
Adinol CT95 [®]	0.16
Lutrol F127	14.00
purified water up to a total weight of 100 %.	

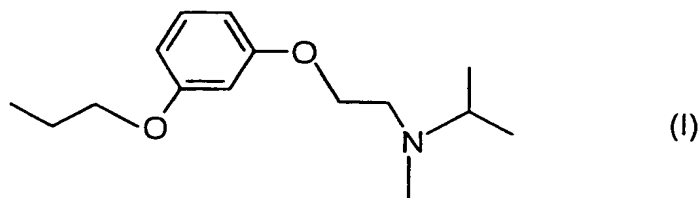
- 10 The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

<u>Example 6</u>	<u>[% by weight]</u>
15 Lidocaine	2.25
Prilocaine	2.25
Arlatone 289 [®]	1.90
Adinol CT95 [®]	0.28
Lutrol F127	14.00
20 purified water up to a total weight of 100 %.	

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

Example 7 and 8

In Examples 7 and 8, a local anaesthetic of the formula (I) was used as the active ingredient.



This compound is disclosed in the International Patent Application SE96/01361.

The following pharmaceutical compositions were prepared.

<u>Example 7</u>	<u>[% by weight]</u>
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Compound (I)	2.5
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Lutrol F127 [®]	17.0
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Lutrol F68 [®]	5.5
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purified water up to a total weight of 100 %.

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

<u>Example 8</u>	<u>[% by weight]</u>
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Compound (I)	2.5
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Lutrol F127 [®]	20.0
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Lutrol F68 [®]	5.5
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purified water up to a total weight of 100 %.

The composition was prepared by following the procedure described above, and the pH-value was adjusted by adding 2 M hydrochloric acid.

5

Biological studies

A pharmaceutical composition according to Example 1 was applied to a human periodontal pocket with a blunt end needle. After an onset time of 30 - 45 seconds, a satisfactory anaesthetic effect had been achieved in order that periodontal scaling could be performed. The scaling was initiated, and the time taken to scale the tooth was noted. At the end of the scaling, the intensity of pain was measured by means of a visual analogue scale (VAS). The duration of the anaesthetic effect was 10-20 minutes.

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Claims

1. A pharmaceutical composition comprising

(i) one or more local anaesthetics in oil form in the final composition;

(ii) one or more surfactants, together present in an amount effective to produce a homogenous formulation; and

(iii) water up to 100 % by weight, based on the total weight of the composition.

2. A pharmaceutical composition according to claim 1, further comprising one or more taste masking agents.

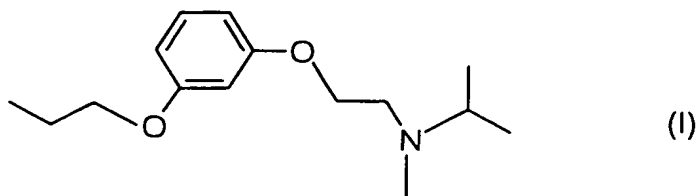
3. A pharmaceutical composition according to claim 1 or 2, wherein the amount of the local anaesthetic or mixture of local anaesthetics is present in an amount of 0.5 - 20 % by weight based on the total weight of the composition.

4. A pharmaceutical composition according to claim 3, wherein the amount of local anaesthetic or mixture of local anaesthetics being present in an amount of 2-7 % by weight based on the total weight of the composition.

5. A pharmaceutical composition according to any of the preceding claims, wherein the active ingredient is a eutectic mixture of local anaesthetics.

6. A pharmaceutical composition according to claim 5, wherein the active ingredient is a eutectic mixture of lidocaine and prilocaine.

7. A pharmaceutical composition according to claim 1, wherein the active ingredient is



5

8. A pharmaceutical composition according to any of the preceding claims, comprising more than one surfactant of which at least one is a surfactant having thermoreversible gelling properties.
- 10 9. A pharmaceutical composition according to any of the preceding claims, the total amount of the surfactant(s) being present in an amount of up to 50 % by weight based on the total weight of the composition.
- 15 10. A pharmaceutical composition according to any of the preceding claims, wherein the surfactant is a non-ionic surfactant.
11. A pharmaceutical composition according to claim 10, wherein the surfactant is a poloxamer.
- 20 12. A pharmaceutical composition according to any of the preceding claims, comprising the two surfactants Lutrol F68[®] and Lutrol F127[®].

13. A pharmaceutical composition according to any of the preceding claims for use in therapy.

14. A pharmaceutical composition according to claim 13, for use as a local anaesthetic administered on the mucosa of the oral cavity.

15. A pharmaceutical composition according to claim 14, the therapeutic indication being pain relief during periodontal scaling.

16. Use of a pharmaceutical composition according to claim 1, for the manufacture of a medicament for pain relief during periodontal scaling.

17. A method for the treatment of pain associated with periodontal scaling, whereby a pharmaceutical composition according to claim 1 is applied to a patient in the need of pain relief during periodontal scaling.

18. A process for the manufacture of a pharmaceutical composition according to claim 1, whereby

(i) the local anaesthetic(s) and the surfactant with the lowest molecular weight if more than one surfactant is used, are melted together;

(ii) a part of the water is slowly added to the melt (i) during homogenization, forming an emulsion concentrate;

(iii) if more than one surfactant is used, the surfactant with the higher molecular weight is dispersed in water;

(iv) the emulsion concentrate of step (ii) and part of the surfactant solution of step (iii) are thoroughly mixed;

(v) the pH-value is adjusted by the addition of a suitable acid or base;

(vi) the weight is adjusted with water to the final weight of the composition.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/00566

A. CLASSIFICATION OF SUBJECT MATTER		
IPC6: A61K 9/06, A61K 47/34, A61K 31/165 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EMBASE, WPI, CLAIMS, CAPLUS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4780320 A (RICHARD W. BAKER), 25 October 1988 (25.10.88), column 3, line 3 - line 10; column 4, line 38 - line 40; column 7, line 26 - line 57, claims --	1-18
X	EP 0455396 A1 (MEDIVENTURES INC.), 6 November 1991 (06.11.91), page 4, line 11 - page 5, line 40; page 6, line 14 - line 16 -- -----	1-18
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
22 July 1997		29 -07- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/00566

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claim 17 are directed to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/07/97

International application No.
PCT/SE 97/00566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4780320 A	25/10/88	AU 614061 B	22/08/91
		AU 7211287 A	05/11/87
		CA 1309345 A	27/10/92
		DE 3787829 D,T	11/05/94
		EP 0244118 A,B	04/11/87
		SE 0244118 T3	
		JP 63027422 A	05/02/88
		NO 177125 B,C	18/04/95
		US 4919939 A	24/04/90
<hr/>			
EP 0455396 A1	06/11/91	SE 0455396 T3	
		CA 2040460 A	02/11/91
		DE 69124416 D	00/00/00
		JP 4225914 A	14/08/92
		US 5300295 A	05/04/94
		US 5593683 A	14/01/97
		US 5306501 A	26/04/94
		US 5292516 A	08/03/94
		US 5298260 A	29/03/94
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